IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of:

Manne Satyanarayana REDDY et al.

Application No.: 10/516,897 Art Unit: 1626

Filed: July 5, 2005 Examiner: Robert H. Havlin

For: 3-[2'-(DIMETHYLAMINO)ETHYL]-N-METHYL-1H-INDOLE-5-METHANE SULFONAMIDE AND THE SUCCINATE THEREOF

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

SUPPLEMENTAL BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed on June 11, 2008 for the subject application, and in response to the Notification of Non-Compliant Appeal Brief that was mailed on September 23, 2008, this brief in support of the appeal is now submitted. Appellants understand that it is only necessary to submit replacements for certain sections of the original brief, submitted on September 11, 2008, to comply with the notification, but certain errors recently noted in that original brief (primarily, errors in the citations of authorities) are now being corrected by this submission of a complete brief.

1. Real Party in Interest

The real parties in interest are Dr. Reddy's Laboratories Limited and Dr. Reddy's Laboratories, Inc., assignees of the application from the inventors/appellants.

2. Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal, or which will affect or have a bearing on this appeal.

3. Status of the Claims

Claims 1-24, 27-30, and 36-47 are pending, with original claims 25, 26, and 31-35 having been canceled by a preliminary amendment.

Claims 1-24, 27-30, and 36-47 were finally rejected in an Office Action mailed on December 12, 2007, and are the subject of this appeal.

4. Status of Amendments

No amendments were submitted following the final rejection. All previously submitted amendments have been entered.

5. Summary of Claimed Subject Matter

Independent claim 1 is directed to crystalline Form I of the drug compound having an adopted name sumatriptan succinate, defined, inter alia, by the X-ray powder diffraction pattern of Fig. 1, other analytical information presented in Figs. 2 and 3, and prepared by processes described in Examples 3-5 (application page 17, line 9 through page 18, line 14).

Independent claim 8 is directed to a process for the preparation of crystalline Form I of sumatriptan succinate, the process being generally described in the application (page 9, line 12 through page 10, line 9).

Independent claim 13 is directed to crystalline Form II of sumatriptan succinate, defined, *inter alia*, by the X-ray powder diffraction pattern of Fig. 4, other analytical

information presented in Figs. 5 and 6, and prepared by processes described in Examples 6 and 7 (application page 18, line 16 through page 19, line 9).

Independent claim 21 is directed to a process for the preparation of crystalline Form II of sumatriptan succinate, the process being generally described in the application (page 10, lines 10-25).

Independent claim 27 is directed to a process for the preparation of highly pure sumatriptan. This process is generally described in the application at page 11, line 18 through page 12, line 4.

Independent claim 36 is directed to crystalline sumatriptan having a purity about 99% or higher by high performance liquid chromatography, and is generally disclosed at page 5, lines 1 and 2.

A copy of the appealed claims is appended hereto, beginning at page 9.

6. Grounds of Rejection to be Reviewed on Appeal

a. Whether claims 1-7, 13-20, 42-44, 45 and 47 are unpatentable under 35 U.S.C. § 102(b) over U.S. Patent No. 5,037,845 to Oxford et al. ("*Oxford*").

b. Whether claims 1-24, 27-30, and 36-47 are unpatentable under 35 U.S.C. § 103(a) over *Oxford* in view of Brittain, Polymorphism in Pharmaceutical Solids, 95, Marcel Dekker (1999) ("*Brittain*"), and further in view of J. G. Dorsey, Liquid Chromatography, McGraw-Hill, http://www.accessscience.com ("*Dorsey*") and Vogel, Practical Organic Chemistry, Wiley, 3rd ed. (1966) ("*Vogel*").

7. Argument

a. Rejection Under 35 U.S.C. § 102(b)

Claims 1-7, 29-30, 42-45, and 47 stand rejected as allegedly anticipated by *Oxford*. The Examiner maintains that *Oxford*'s Example 19 describes a solid identical to the succinate salt of sumatriptan claimed in the application on appeal. On this ground, the Examiner suggests that *Oxford* inherently anticipates the claimed forms of sumatriptan succinate.

First, to establish a *prima facie* case of inherent anticipation, the Examiner must show scientific rationale or objective evidence tending to show inherency. *See* MPEP

§2112. *See also Ex parte Reguri*, Appeal No. 2007-0313 for Application No. 10/414,447 (Bd. Pat. App. & Inter. 2007), at 4. Only then the burden will shift to the Appellants to disprove the inherency. *Id.*, *citing*, *Ex parte Skinner*, 2 USPQ2d (BNA) 1788 (Bd. Pat. App. & Inter. 1986).

Appellants make reference to the decision of the Board of Patent Appeal and Interferences in *Ex parte Reguri*. The facts of the application on appeal are quite similar to the facts of *Reguri*. Similarly to *Reguri* and *Skinner*, the facts do not justify shifting the burden. *See also Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254, now U.S. Patent No. 6,452,007 (Bd. Pat. App. & Inter. 2001) ("The examiner has provided no evidence or scientific reasoning to show that the delavirdine mesylate disclosed and claimed [in the prior art reference] is in the [claimed] crystal form. Therefore, the examiner has not made out a *prima facie* case of anticipation by inherency" [*text in brackets added*]). While *Oxford* discloses a crystalline form of sumatriptan succinate, the rejected claims recite particular polymorphs, namely Forms I and II of sumatriptan succinate. The Examiner did not set forth adequate objective evidence or scientific reasoning that supports a conclusion that the polymorphic form of *Oxford* and the claimed Forms I and II are the same. In fact, the evidence in the file wrapper indicates to the contrary. In the present case, as in *Reguri*, the preparation methodologies disclosed in the specification of the application on appeal are different from the prior art (the Example 19 of *Oxford*). *Compare Ex parte Reguri*, at 4. *Oxford*'s Example 19 discloses crystallization of sumatriptan succinate from IMS (industrial methylated spirits). *See Oxford*, col. 26, ln. 12. The solvents used to precipitate the presently claimed Forms I and II are different. *Compare Ex parte Reguri*, at 4 (using the evidence of difference in preparation methodologies between the prior art and the invention to find absence of *prima facie* case of inherency).

Second, to establish inherency, the reference's teachings or extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and it would be so recognized by persons of ordinary skill." *See* MPEP §2112, *citing In re Robertson*, 49 USPQ2d (BNA) 1949, 1950-51 (Fed. Cir. 1999). Not only the missing matter, namely, the polymorphic form of sumatriptan succinate, is not "necessarily present" in *Oxford*, but the comparison of analytical data

(X-ray powder diffraction, infrared absorption) informs one skilled in the art to the contrary, namely that the crystalline form of *Oxford* differs from Forms I and II claimed in the application on appeal. Appellants make reference to Examiner's own superimposition of Figures 1 and 7 (for X-ray powder diffraction analysis) and Figures 3 and 8 (for infrared analysis). *See* Final Office Action, pages 3 and 4. Even at a glance, the superimpositions of the spectral data demonstrate numerous differences in peak location and intensity. Even assuming, *arguendo*, that the burden should shift, Appellants would be at a loss as to how they could be expected to demonstrate the differences in another manner. Likewise, the melting points of the claimed Forms I and II and the crystalline form of *Oxford* are different. The major endo peak in a differential scanning calorimetry thermogram for Form I is 169°C (Figure 2). The major endo peak in a differential scanning calorimetry thermogram for Form II is 168°C (Figure 5). *Oxford*'s reported melting point for its crystalline form is 164-165°C. *See Oxford*, col. 26, ln. 19. Compare *Ex parte Reguri*, at 4 (finding that a *prima facie* case of inherency has not been established, based, in part, on evidence of differences in physical properties, and melting points in particular (105-115°C for the prior art and 91-102°C for one of the claimed polymorphs)).

Accordingly, Appellants submit that claims 1-7, 29-30, 42-45, and 47 are not anticipated by *Oxford*, and the rejection should not be sustained.

b. Rejection Under 35 U.S.C. § 103(a)

Claims 1-24, 27-30, and 36-47 stand rejected as obvious over *Oxford* in view of secondary references. For example, the Examiner suggests that since *Brittain* teaches the desirability of screening for polymorphs, all new polymorphs are *prima facie* obvious. The Examiner stated:

> Again, the only apparent difference in the product produced by the process claimed in the instant application is the use of a solvent other than industrial methylated spirits (IMS as indicated in Oxford). IMS is actually a mixture primarily of ethanol with methanol added and one of ordinary skill in the art is aware that it is a good crystallization solvent. Thus one of ordinary skill in the art immediately would know to look to alternate solvent.

See final Office Action, at page 5. In essence, the Examiner suggests that any new polymorph of a known compound is *prima facie* obvious, absent showing of unexpected results, because an artisan is expected to look for polymorphs.

According to MPEP § 706.02(j):

> To support the conclusion that the claimed invention is directed to obvious subject matter, either the references must expressly or impliedly suggest the claimed invention or the examiner must present a convincing line of reasoning as to why the artisan would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 USPQ 972, 973 (Bd. Pat. App. & Inter. 1985).

Recent decisions of the United States Court of Appeals for the Federal Circuit and Board of Patent Appeals and Interferences continue to require, as a basis of finding obviousness, a reason for one skilled in the art to modify the prior art in the direction of claimed invention. *See, e.g., Ortho McNeil Pharm., Inc. v. Mylan Laboratories, Inc.*, 520 F.3d 1358, 1364 ("… a flexible TSM test remain a primary guarantor against non-statutory hindsight analysis …"); *In re Translogic Tech, Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007); *Ex parte Reguri*.

The file wrapper of the application on appeal includes evidence that strongly suggests that an artisan will not have a reasonable expectation of success when setting out to make new polymorphs of an existing compound. There is no "standard" way to proceed toward making a new polymorphic form of a compound. Thus, the file wrapper of this application contains: a) an article by A. Goho, "Tricky Business," *Science News*, Vol. 166(8), 2004, in the form of an eight-page web reprint; b) an article by J. Dunitz et al., "Disappearing Polymorphs," *Accounts of Chemical Research*, Vol. 28, pp. 193-200 (1995); and c) an article by R. J. Davie, "Pizzas, Polymorphs, and Pills," *Chemical Communications, 2003*, pp. 1463-1467. The articles were submitted to the Examiner by Appellants on October 16, 2007 and describe instances of discovery of new polymorphs of old compounds after considerable periods of time, and disappearances of a previously identified polymorph. Together, these articles illustrate the present state of the art and show that, at the present time, prediction of the existence of a polymorph, and the prediction of a specific polymorphic state, are not possible. *See* MPEP §2142,

citing, *inter alia*, *In re Rinehart*, 531 F.2d 1048, 189 USPQ (BNA) 143 (CCPA 1976) ("Evidence showing there was no reasonable expectation of success may support a conclusion of non-obviousness"). Based on this evidence, Appellants maintain that existence of one crystalline form of a solid (*i.e.*, the solid produced in the Example 19 of *Oxford*) provides no reasonable expectation of success to make any new polymorph, let alone to make the specific polymorph claimed. Appellants note it is the latter that is required: there must be a reasonable expectation of success to make the invention, *i.e.*, the specifically claimed polymorph. While Appellants are well aware of the decision of the United States Supreme Court in *KSR Int'l v. Teleflex, Inc*. 127 S.Ct. 1727 (2007), the facts of the present case have nothing to do with a situation where "there are a finite number of identified, predictable solutions," when "a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp." *KSR Int'l* at 1742. As the evidence regarding the state of the art as a whole shows, the universe of various solvents, polymorphic forms, and/or precipitation conditions is neither finite nor predictable.

In *Reguri*, the Board of Patent Appeals and Interferences has rejected a conclusion of obviousness under the facts greatly similar to the facts in the application on appeal. In *Reguri*, the Examiner cited Cheronis as a secondary reference to show that use of re-crystallization is well know in the art and finding obviousness of the basis of combining Cheronis with a primary reference that taught a crystalline solid. In other words, the Examiner in *Reguri* argued that since re-crystallization is known, an artisan would employ it to arrive at the claimed polymorph. The Board rejected this reasoning, stating that while one would be expected to purify by crystallization, "that would not necessarily lead to the claimed crystalline forms." *Id.* at 5. It is precisely one of the issues in the application on appeal. While an artisan may be expected to search for polymorphs (as arguably suggested by *Brittain*), an artisan will not have a reasonable expectation of success in finding any polymorph, and will certainly not have such expectation with respect to the specific polymorph claimed.

Further, there is no teaching or suggestion in *Oxford*, secondary references, or anything of evidence in the file wrapper that sumatriptan succinate specifically may exist in a polymorphic form other than the one obtained in Example 19. Thus, the prior art as

a whole provides no reason to modify the solid of *Oxford* in a direction toward the claimed polymorphs. *KSR Int'l* at 1742 (stating that finding of obviousness is expected to be based on a conclusion that the prior art provides an "apparent reason" for a combination or modification). *See also Ex parte Havens*, Appeal No. 2001-0091 for Application No. 08/732,254, now U.S. Patent No. 6,452,007 (Bd. Pat. App. & Inter. 2003) ("The examiner's obviousness rejection seems to suffer the same infirmity as her anticipation rejection . . . The examiner has provided no evidence or convincing reason why the prior art disclosure of delavirdine mesylate in an undefined state would have suggested the specific S and T crystal forms that are the subject of the instant claims.") [*emphasis added*].

Accordingly, Appellants submit that the rejected claims 1-24, 27-30, and 36-47 are not rendered *prima facie* obvious by *Oxford* in view of *Brittain*, and further in view of *Dorsey* and *Vogel*, and this rejection should not be sustained.

CONCLUSION

Appellants submit that claims 1-24, 27-30, and 36-47 meet the requirements for patentablility under 35 U.S.C. §§ 102 and 103. Accordingly, reversal of the Examiner's rejections is appropriate and is respectfully solicited.

Respectfully submitted,

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September 30, 2008

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CLAIMS APPENDIX

1. A crystalline Form-I of Sumatriptan succinate.

2. A crystalline Form-I of Sumatriptan Succinate according to claim 1 having X-ray powder diffraction pattern with peaks about 12.628, 13.256, 15.412, 15.704, 16.198, 16.397, 18.107, 19.894, 20.061, 20.243, 20.582, 21.353, 22.734, 26.018 and 26.938 two-theta degrees.

3. A crystalline Form-I of Sumatriptan succinate of claim 1 which has X-ray powder diffraction pattern substantially as depicted Figure (1).

4. A crystalline Form-I of Sumatriptan succinate of claim 1 which has a Differential Scanning Calorimetry thermogram, which exhibits a significant endo peak about 169ºC.

5. A crystalline Form-I of Sumatriptan succinate of claim 1 which has a Differential Scanning Calorimetry thermogram substantially as depicted in Figure (2).

6. A crystalline Form-I of Sumatriptan succinate of claim 1 having identified characteristic bands about 3373, 3101, 2932, 1708, 1566, 1338, 1299, 1270, 1170, 1081, 884 and 638 cm^{-1} in Infra red spectrum.

7. A crystalline Form-I of Sumatriptan succinate of claim 1 having an Infra red spectrum substantially as depicted in Figure (3).

8. A process for the preparation of crystalline Form-I of Sumatriptan succinate, which comprises;

a) treating highly pure Sumatriptan base in a ketone solvent selected from the group consisting of acetone, methyl isobutyl ketone and methyl ethyl ketone; or an ether solvent selected from the group consisting of tetrahydrofuran, diethyl ether,

diisopropyl ether and diisobutyl ether, or an ester solvent selected from the group consisting of methyl acetate, ethyl acetate, propyl acetate and butyl acetate, or an alcoholic solvent selected from the group consisting of methanol, propanol, isopropanol, butanol, isobutanol, and mixtures thereof;

b) adding Succinic acid to the reaction mixture;

c) optionally concentrating the reaction mixture;

d) cooling the reaction mixture to a temperature of 0-35ºC; and

e) filtering the isolated solid accompanied by drying the solid at a temperature of 50-100ºC to afford the crystalline Form-I of Sumatriptan succinate.

9. The process as claimed in claim 8 wherein the ketone solvent of step (a) is acetone.

10. The process as claimed in claim 8 wherein the ether solvent is of step (a) is tetrahydrofuran.

11. The process as claimed in claim 8 wherein the ester solvent of step (a) is ethyl acetate.

12. The process according to claim 8 wherein the highly pure Sumatriptan is at least about 99% pure by HPLC.

13. A crystalline Form-II of Sumatriptan succinate.

14. A crystalline Form-II of Sumatriptan Succinate according to claim 13 having X-ray powder diffraction pattern with peaks comprising about 7.320, 18.751, 19.047, 19.966, 26.089, 29.675 and 31.474 two-theta degrees.

15. A crystalline Form-II of Sumatriptan succinate of claim 13 which has an X-ray powder diffraction pattern substantially as depicted in Figure (4).

16. A crystalline Form-II of Sumatriptan succinate of claim 13 which has a Differential Scanning Calorimetry thermogram, which exhibits a significant major endo peak about 168°C, and minor endo peaks about 122°C and 160°C.

17. A crystalline Form-II of Sumatriptan succinate of claim 13 which has a Differential Scanning Calorimetry thermogram substantially as depicted in Figure (5).

18. A crystalline Form-II of Surnatriptan succinate of claim 13 having infrared characteristic bands at about 3358, 3268, 2931, 1707, 1569, 1336, 1301, 1264, 1143, 1092, 884 and 639 cm^{-1} in Infra red spectrum.

19. A crystalline Form-II of Sumatriptan succinate of claim 13 having an Infrared spectrum substantially as depicted in Figure (6).

20. A crystalline Form-II of Sumatriptan Succinate according to claim 13 having X-ray powder diffraction pattern with a peak about 7.320 two-theta degrees and a Differential Scanning Calorimetry thermogram, which exhibits a significant major endo peak about 168°C, and minor endo peaks about 122°C and 160°C.

21. A process for the preparation of a crystalline Form-II of Sumatriptan succinate, which comprises;

a) refluxing highly pure Sumatriptan in an aliphatic/alicyclic hydrocarbon solvent or a halogenated solvent;

b) adding Succinic acid to the reaction mixture;

c) refluxing the reaction mixture with Succinic acid;

d) cooling the reaction mixture after the step (c); and

e) isolating separated solids to afford crystalline Form-II of Sumatriptan succinate.

22. A process as claimed in claim 21 of step (a), wherein the alicyclic hydrocarbon solvent is cyclohexane.

23. A process as claimed in claim 21 wherein the halogenated solvent of step (a) is dichloromethane.

24. A process according to claim 21 wherein the highly pure Sumatriptan is at least about 99% pure by HPLC.

25. (Canceled)

26. (Canceled)

27. A process for the preparation of highly pure N-Methyl-3- [2-(dimethylamino) ethyl]-1H-Indole-5 methane sulfonamide (Sumatriptan), which comprises;

a. dissolving crude Sumatriptan in acetone to form a clear solution;
b. treating the obtained clear solution with charcoal;
c. concentrating the clear filtered solution to about filterable volume level;
d. cooling the reaction mixture to a temperature of 0-30ºC; and
e. isolating the obtained solid.

28. The process according to claim 27 wherein the highly pure Sumatriptan is at least about 99% pure by HPLC.

29. A composition comprising a crystalline Form I of Sumatriptan succinate as defined as in claim 1 and one of more pharmaceutically acceptable carrier.

30. A composition comprising a crystalline Form II of Sumatriptan succinate as defined as in claim 13 and one of more pharmaceutically acceptable carrier.

31. (Canceled)

32. (Canceled)

33. (Canceled)

34. (Canceled)

35. (Canceled)

36. A crystalline form of sumatriptan base having a purity of about 99% or higher by HPLC.

37. A crystalline form of sumatriptan base according to claim 36, wherein said purity is about 99.5% or higher by HPLC.

38. A crystalline form of sumatriptan base according to claim 36, wherein said purity is about 99.7% or higher by HPLC.

39. A crystalline form of sumatriptan base according to claim 36, wherein said crystalline form of sumatriptan base has any unknown purity about 0.1% or less.

40. A crystalline form of sumatriptan base according to claim 36, wherein said crystalline form has an X-ray powder diffraction pattern substantially the same as Figure 7.

41. A crystalline form of sumatriptan base according to claim 36, wherein said crystalline form has an infrared spectrum substantially the same as Figure 8.

42. The crystalline Form-II of Sumatriptan succinate according to claim 14, wherein said peaks further comprise 14.707 and 22.904 two-theta degrees.

43. A composition comprising the crystalline form of sumatriptan base as defined as in claim 36 and one or more pharmaceutically acceptable carrier.

44. A method for treating a migraine comprising administering an effective amount of the compound of claim 1.

45. A method for treating a migraine comprising administering an effective amount of the compound of claim 15.

46. A method for treating a migraine comprising administering an effective amount of the compound of claim 36.

47. A compound of sumatriptan base prepared according to claim 27.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

None.